Original Article

Solubility Enhancement Of Ketoprofen Drug By Preparing Lipids Based Formulation

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Abstract

The objective of this study was aimed at designing Ketoprofen capsule formulations with improved solubility of a practically water insoluble drug, with the intent of achieving a formulation with significantly improved in vitro drug dissolution profile in comparison to reference product Redufen®. Several combinations of surfactant, oil and co- solvent try to designs capsule having supra solubility, by tailoring their combination with the objective to obtain this. The concept of increasing the solubility by virtue of application of a combination of the medium chain triglycerides and polysorbate 80 having high HLB value and ethyl acetate act as co- solvent and stabilizer for the emulsion thus arriving at compositions C4. *In vitro* dissolution studies on these capsules demonstrated that C4 was the most appropriate formulation with regards to its closeness in enhanced drug solubility when compared to Redufen®. Accelerated stability study on the C4 composition in HDPE packaging further demonstrated that no adverse changes occur in the optimized formulation when evaluated for parameters such as Disintegration time, drug content and *in vitro* dissolution.

Keywords- Ketoprofen, Medium chain triglycerides, Polysorbate 20, Cremophor RH-40

INTRODUCTION

The chief objective is to design and formulate a dosage form possessing optimum therapeutic efficacy of drug, economical production on large scale and prolonged shelf-life of the drug. Poor solubility of a drug is in most cases associated with poor bioavailability. The goal of an oral lipid-based formulation is to improve the bioavailability of a poorly water-soluble drug to an extent greater than that achievable with a conventional oral solid dosage form. Lipids is defined as hydrophobic or amphiphilic small molecules which are naturally occurring and semisynthetic molecules includes fatty acid, fatty alcohol, wax and phospholipids etc. The amphiphilic nature of some lipids allows them to form structures such as micelles, vesicles and liposomes etc. in an aqueous environment.[1]

The primary mechanism by which lipid-based formulations enhance bioavailability is through solubilization of the drug. There are number of lipids available for formulations. Despite the number of possibilities, only a relatively small subset of lipids has found application in clinical formulation development due to a limited or nonexistent history of pharmaceutical application or, more commonly, a lack of regulatory approval. currently marketed classes of lipid excipients are as follows: [2]

- Fatty acids
- Natural oils and fats
- Polyglyceryl Fatty Acid Esters
- Cholesterol and phospholipids

MATERIALS AND METHODS

Model Drug – Ketoprofen

Ketoprofen is an anionic non-steroidal anti-inflammatory drug (NSAID). It is a derivative of propionic acid and widely used in the management and treatment of patients with rheumatic disease. Gift sample of Ketoprofen (B. No. PX/001/7010, Mfg. Jun. 2007 and retest date May 2010) manufactured by Ami Life Sciences was provided by M/s Inventia Healthcare Pvt. Ltd., Thane.

Excipients

The various excipients used in the preparation of Ketoprofen capsule are indicated in table 2.1. The table also indicates their intended function in the formulation.

TABLE 1.1 Excipients used for the Preparation of Ketoprofen capsule

	Excipients	Make or Grade	Function in Formulation
Excipients used to improve solubility and bioavailability			
1.	**Oils**		
•	Medium chain triglycerides	Captex® 300	Solubilise the lipophilic drug
•	Lemon Oil	Bergamot® Oil	
•	Corn oil	Puerco®	
•	Olive oil	Pomace®	
•	Hydrogenated Soybean oil	sterotex®	
2.	**Surfactant/ Co-Surfactant**		
•	Polysorbate 20	SD fine chem	Helpful for the immediate formation of emulsion
•	Polysorbate 80	SD fine chem	
•	Sorbitan mono oleate	SD fine chem.	
•	Cremophor RH-40	BASF	
	Cremophor EL	BASF	
3.	**Co-Solvent**		
•	Ethanol	Hayman	Help to dissolve hydrophilic surfactant or hydrophobic drug in lipid base
•	Ethyl acetate	Qualigen	
•	Propylene Glycol	Merck	
•	Polyethylen Glycol	Clariant	
4	**Empty hard gelatine capsule** (Flo- Fit capsule)	ACG	

The various equipments used in the present study with their purpose are indicated in table 1.2

Table 1.2 (Equipment used)

S. No.	Equipment	Purpose
1.	Homogenizer/ Stirrer	Mixing
2.	Micropipette	Capsule filling
3.	Capillary tubes	Sealing of capsule

Steps involved in Preparation of Ketoprofen capsule Design of Ketoprofen capsule involved following steps –
1. Design, composition and preparation of enhanced solubility and bioavailability of Ketoprofen capsule.
2. Design, composition and preparation of Ketoprofen capsule solution.

The present study was designed to evaluate and compare the efficacy of capsules against innovator hence product design was aimed at preparing liquid filled capsule of Ketoprofen to achieve drug release in vitro that is comparable to that of reference/innovator product.

Preparation of Ketoprofen capsule
Ketoprofen capsule were prepared by mixing the combination of the oils like lemon, different surfactant/co surfactant and some key excipients. The qualitative and quantitative compositions of different prototype formulation were as under.

1. ***Prototype Formulation A*** – These formulations contained combination of oils like lemon oil, different surfactant/co surfactant and co solvent as the vehicle and as a solubility enhancer
2. ***Prototype Formulation B*** – These formulations contained combination of oils like hydrogenated soya bean oil, different surfactant/co surfactant and co solvent as the vehicle and as a solubility enhancer
3. ***Prototype Formulation C*** – These formulations contained combination of oils like medium chain triglycerides, different surfactant/co surfactant and co solvent as the vehicle and as a solubility enhancer.

Detailed compositions of these prototype formulations are given in table 1.3.

TABLE 1.3 Compositions for the Preparation of immediate-Release Ketoprofen capsule

Prototype Formulation A						
		Quantity(gm)				
Sr. No	**Excipients**	**A1**	**A2**	**A3**	**A4**	**Function**
1	Ketoprofen	100	100	100	100	Active
2	Lemon oil	170	170	170	170	Oils
3	Polysorbate 80	----	130	----	130	Surfactant
4	Cremophor EL oil	130	-----	130	------	Surfactant
5	Ethanol	200	200	-------	-------	Co-solvent
6	Ethyl acetate	----	-----	200	200	Co-solvent
	Total weight	600	600	600	600	

Prototype Formulation B						
		Quantity(gm)				
Sr. No	**Excipients**	**B1**	**B2**	**B3**	**B4**	**Function**
1	Ketoprofen	100	100	100	100	Active
2	Hydrogenated soybean oil	170	170	170	170	Oils
3	Polysorbate 80	----	130	----	130	Surfactant
4	Cremophor EL oil	130	-----	130	------	Surfactant
5	Ethanol	200	200	-------	-------	Co-solvent
6	Ethyl acetate	----	-----	200	200	Co-solvent
	Total weight	600	600	600	600	

Prototype Formulation C						
		Quantity(gm)				
Sr. No	**Excipients**	**C1**	**C2**	**C3**	**C4**	**Function**
1	Ketoprofen	100	100	100	100	Active
2	Medium chain triglycerides	170	170	170	170	Oils
3	Polysorbate 80	----	130	----	130	Surfactant
4	Cremophor EL oil	130	-----	130	------	Surfactant
5	Ethanol	200	200	-------	-------	Co-solvent
6	Ethyl acetate	----	-----	200	200	Co-solvent
	Total weight	600	600	600	600	

RESULT AND DISCUSSION

In the present study, an attempt was made to design and evaluate Ketoprofen capsule with the prime objective of to enhance the solubility of Ketoprofen and to match or have a better *in vitro drug dissolution* profile. The prototype C 3 containing oil medium chain triglycerides, surfactant cremophor EL and co solvent ethyl acetate show greater dissolution in the different media as compared to the prototype. This combination have on the contact with dissolution media form clear, isotropic mixture which facilitate the lymphatic absorption which avoid the first pass hepatic metabolism. The optimized capsule formulations were suitably packaged in HDPE and subjected to accelerated stability testing as per the ICH guidelines. The subsequent paragraph discusses the results obtained from the present investigations.

2.1 Physical Attributes of Ketoprofen capsuleDisintegration Time

Water was use as the immersion fluid for testing the disintegration time of the Ketoprofen immediate release capsule; previously maintain the temperature of the immersion fluid 37. Placed the capsule in each of the six tubes of the basket with disc, run the apparatus, record the time to rupture the capsule, confirm the complete disintegration by lifting the basket from the fluid and observe all of capsules have disintegrated completely.

TABLE 2.1. Disintegration Time of immediate Release capsule of Ketoprofen

Parameters	**Prototype formulations**											
	A1	**A2**	**A3**	**A4**	**B1**	**B2**	**B3**	**B4**	**C1**	**C2**	**C3**	**C4**
Disintegration Time (min)	2.13	2.57	2.42	3.08	2.58	2.31	2.55	3.09	3.12	2.54	2.50	2.32

Uniformity of weight:

Randomly 20 capsules were selected and intact capsules were weighed individually. Then capsules were cut open by means of clean and dry cutter or blade. Contents of each capsule were removed and capsule shells were washed with dichloromethane (Capsules were labelled for identity). Occluded solvent was allowed to evaporate from shell till the odour is no longer detectable. Emptied capsules weighed individually and calculated the weight of capsules content by subtracting weight of capsule shell from intact capsule weight.

TABLE 2.2 Uniformity of content of immediate Release capsule of Ketoprofen

Parameters	**Prototype formulations**											
	A1	**A2**	**A3**	**A4**	**B1**	**B2**	**B3**	**B4**	**C1**	**C2**	**C3**	**C4**
Average weight (mg)	603	598	598	597	602	596	603	601	603	599	600	604

Particle size study:

Particle size of the prepared solution was studied by particle size counter Zetasizer Nano ZS (Malvern). The prepared solution was diluted with polar solvent (water) where it forms a slight milky appearance and then filled in a glass cuvettewith round aperture. This cuvette was then subjected in the zetasizer for the measurement. Measurement cycle ran by selecting following parameter.

- Dispersant name: Polar solvent (water)
- Temperature: 25° C
- Measurement cycle duration: 60 sec.
- Count rate: 346.8 (kcps)
- Measurement position: 1.25 mm

➢ Attenuation: 5

The result of the particle size count of each of the formulation is illustrated in table 2.3

TABLE 2.3 Particle size count of different prototype solutions of Ketoprofen

Parameters	Prototype formulations											
	A1	A2	A3	A4	B1	B2	B3	B4	C1	C2	C3	C4
Particle size D90 (nm)	223.6	198. 4	119.7	142. 1	278.9	284.6	250.3	262.1	127. 5	136.2	79.2	98.3

All the prepared capsule formulations of Ketoprofen have satisfactory physical characteristics and were mechanically strong enough to withstand the rigors of handling, packaging, storage and transportation also disintegrates within 30 min

2.4. In Vitro Dissolution Profile of Ketoprofen capsule

Results of *in vitro* dissolution of immediate release capsule of Ketoprofen along with fenoglide are given in table 2.4.

TABLE 2.4 Amount of Drug released from Ketoprofen capsule in comparision with that from Redufen

	Sampling interval (min)	Amount Dissolved (%) from Various Prototypes *				
		Redufen	A1	A2	A3	A4
Prototype formulations A	15	39.59	59.6	64.2	34.78	82.5
	30	57.87	68.1	77.1	73.57	92.6
	45	72.76	75.3	83.4	78.20	95.8
	60	82.86	80.2	91.1	79.01	99.3
	120	100.01	84.7	95.7	80.03	100.87
*f*2			51.01	50.91	51.02	50.65

	Sampling interval (min)	Amount Dissolved (%) from Various Prototypes *				
		Redufen	B1	B2	B3	B4
Prototype formulations B	15	39.59	32.3	42.12	39.45	23.89
	30	57.87	41.8	58.02	48.23	54.23
	45	72.76	56.4	69.34	62.34	59.23
	60	82.86	62.7	80.34	75.08	67.01
	120	100.01	65.8	92.12	83.67	81.23
*f*2			50.78	51.46	51.08	50.93

	Sampling interval (min)	Amount Dissolved (%) from Various Prototypes *				
		Redufen	C1	C2	C3	C4
Prototype formulations C	15	39.59	36.43	37.71	39.11	88.91
	30	57.87	45.19	48.087	56.29	98.90
	45	72.76	61.22	68.72	69.02	100.23
	60	82.86	67.07	77.45	80.24.	100.19
	120	100.01	73.19	82.59	98.73	100.56
*f*2			50.89	51.12	51.69	50.59

**Results are mean of 6 readings*

Graphical representation of drug release is depicted in figures

Figure 2.1. Comparative in vitro dissolution profile of Ketoprofen Prototype formulations A Vs Redufen

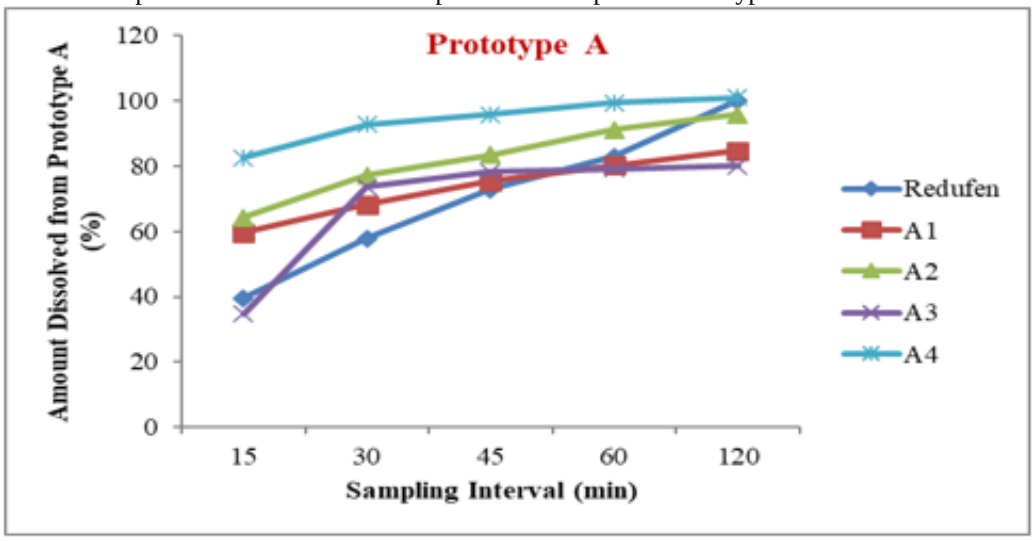


Figure 2.2 Comparative in vitro dissolution profile of Ketoprofen Prototype formulations B Vs Redufen

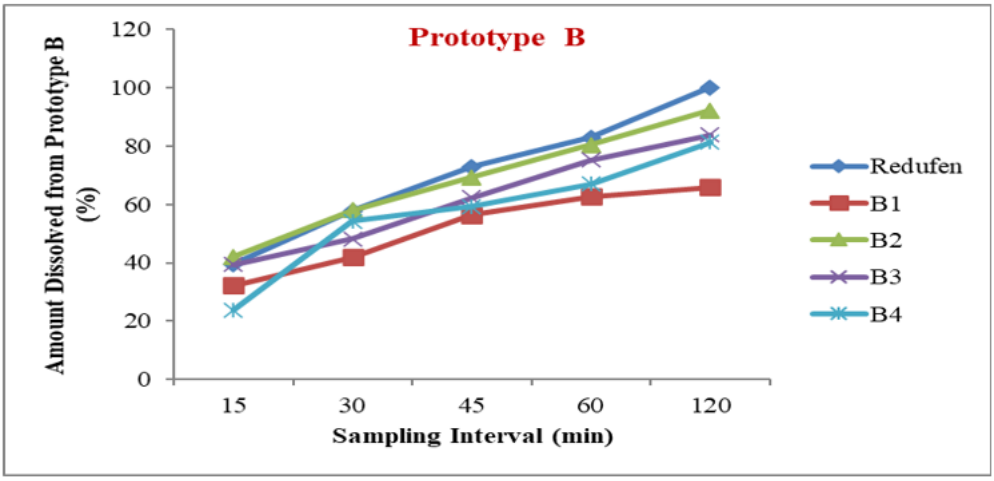
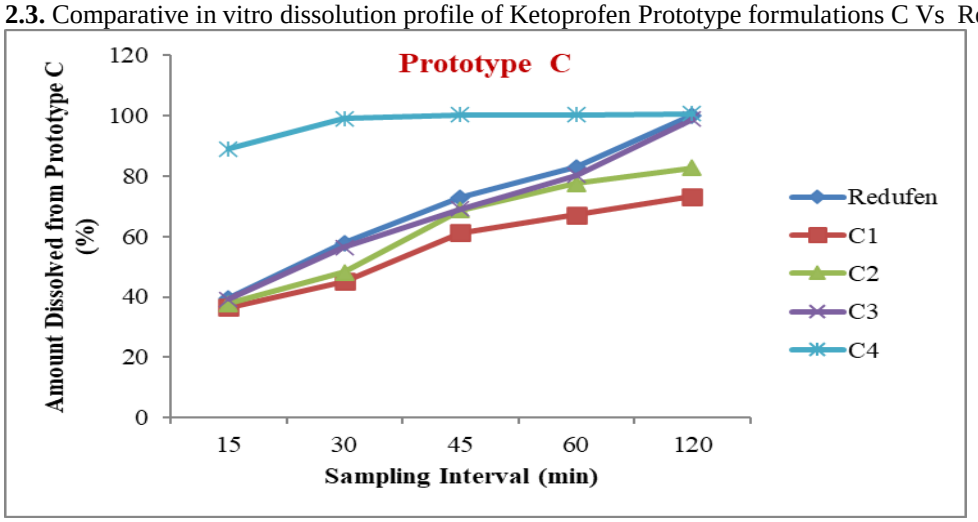


Figure 2.3. Comparative in vitro dissolution profile of Ketoprofen Prototype formulations C Vs Redufen



A direct influence of combination of different oil, surfactant and co-solvent, on the drug release of immediate release capsule of Ketoprofen was observed. All the tested Prototype formulations A1 through A4 containing combination of the lemon oil and surfactant and co-solvent like ethanol and ethyl acetate, demonstrated drug release was dependent upon the type of oil and surfactant combination. The ones that contained lemon oil and cremophor EL combination (formulation A3 and A1) showed slower drug release. In case of formulation A3, which contained ethyl acetate as the co-solvent where as formulation A1 contain ethanol. The prototype A2 and A4 containing combination of polysorbate 80 and lemon oil have ethanol and ethyl acetate as co- solvent in the respective prototype. A4 prototype gives greater drug release.

Prototype B1 through B4 containing combination of the hydrogenated soybean oil and surfactant and co-solvent like ethanol and ethyl acetate, prototype contained hydrogenated soybean oil and cremophor EL combination in the formulation B1 where as formulation B4 contain soybean and polysorbate 80 . In case of formulation B4, which contained ethyl acetate as the co-solvent where as formulation B1 contain ethanol Prototype B1 showed slower drug release. The prototype B2 and B3 containing combination of polysorbate 80 and hydrogenated soybean oil having ethanol give greater drug release.

In case of prototype formulations C that contained combination of medium chain triglycerides, surfactant and co-solvent. The prototype C4 gives above 80% drug release within 15 min this prototype contain surfactant polysorbate 80 and ethyl acetate as co solvent. All the tested prototype f demonstrated the enhancement of the drug release was dependent upon the combination of the surfactant with oil and co- solvent. Thus the system containing the combination of polysorbate 80and medium chain trigycerides along with co- solvent ethyl acetate gives higher drug release which is supra to Redufen.

2.4.1 Stability Studies

After one and three months of storage at 40°C and 75% RH in HDPE container, the moisture content of Ketoprofen capsule formulation remained almost at the initial level of less than 2.0% w/w (at 105°C). Ketoprofen content and *in-vitro* dissolution of stability samples were analysed and showed little or no change in drug release and Ketoprofen content at elevated storage condition as given in table 2.5 which is indicative of good stability of the dosage form in HDPE container.

TABLE 2.5 (Stability Data of Prototype Formulation C4)

	Appearance	Assay (%)	*In-vitro* dissolution (% release)				
			15 min	30 min	45 min	60 min	120 min
Initial	Golden colored transperant capsule	100.30	88.9	98.90	100.23	100.19	100.56
1M - 40°C/ 75%RH	No change	99.51	86.2	97.28	98.97	99.56	99.12
3M - 40°C/ 75%RH	No change	98.76	84.81	96.07	97.09	98.15	98.90

CONCLUSIONS

The present study was aimed at designing Ketoprofen capsule formulations with improved solubility of a practically water insoluble drug, with the intent of achieving a formulation with significantly improved in vitro drug dissolution profile in comparison to reference product Redufen®.

Thus, the composition of formulation which were designed in the present study to arrive at a formulation that shows supra drug solubility to Redufen® were as under –

- Medium chain triglycerides combination (Oil)
- Polysorbate 80 combination (Surfactant)
- Ethyl acetate (Co- solvent)

Several combination of surfactant, oil and co- solvent try to designs capsule having supra solubility, by tailoring their combination with the objective to obtain this. The concept of increasing the solubility by virtue of application of an combination of the medium chain triglycerides and polysorbate 80 having high HLB value and ethyl acetate act as co-solvent and stabalizer for the emulstion thus arriving at compositions C4. *In vitro* dissolution studies on these capsules demonstrated that C4 was the most appropriate formulation with regards to its closeness in enhanced drug solubility when compared to Redufen® . Accelerated stability study on the C4 composition in HDPE packaging further demonstrated that no adverse changes occur in the optimized formulation when evaluated for parameters such as Disintegration time, drug content and *in vitro* dissolution.

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